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Splenectomy in Transfusion Dependant Thalassemia - Insights from an Urban Tertiary Care Center Experience

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Abstract

Background: Transfusion dependent Thalassemias require frequent blood transfusions for their well-being. Damaged or defective red blood cells are normally eliminated in the spleen. In Thalassemia there is a large quantity of defective red blood cells leads to an enlarged hyper functioning spleen. Splenectomy may thus prolong red blood cell survival & ultimately result in the reduced need for blood transfusions. However, it is associated with considerable long-term complications, including sepsis, thrombosis, and pulmonary hypertension. This study was conducted to study the indications, the long-term complications, and causes of mortality among patients with TDT who have undergone splenectomy in a low- and middle-income country (LMIC).

Methods: Data was analysed retrospectively from the hospital records of transfusion dependent Thalassemia patients who underwent splenectomy between July 2017 to January 2024, Data collected included demographic and clinical characteristics, haematological parameters, transfusion requirements before splenectomy and at the last follow-up after splenectomy, complications, and mortality causes were studied.

Results: Total data from 15 patients who underwent spleectomy were analyzed. Among these individuals, 11 were diagnosed with Thalassemia Major, 3 with Thalassemia Intermedia, and 1 presented with Hb-E--Beta Thalassemia. The median age at splenectomy was 14years (range 6–22). All of them underwent open splenectomy. The yearly transfusion volume decreased from 258 ml/kg pre-splenectomy (range 180−370) to 145 (range 140 –250)) post-splenectomy at the last follow-up, $p < 0.001$. Two patients were completely transfusion-free at the last follow-up. Complications included pulmonary hypertension in 3 (20 %), thrombosis in 2(13.3 %), and overwhelming post-splenectomy infection in 1 (6.6 %). The iron-overload-related complications included cardiomyopathy in 6 (40%), endocrinopathy in 4 (26.6%) and chronic liver disease in 3 (20 %). Only one patient died within one year of overhelming sepsis due to post spleenectomy.

Conclusion: In our cohort Splenectomy improved mean Hemoglobin, cytopenias with reduction in mean PRC requirement without significant increase in morbidity/mortality. However decision of splenectomy should be individualized, considering risk benefit ratio.

Keywords; Transfusion-dependent thalassemia, Splenectomy, Pulmonary hypertension, Thrombosis, Overwhelming post-splenectomy infection

Introduction

Thalassemia is a group of inherited disorders caused by reduced or absent globin chain production. This leads to imbalanced globin chains in the red blood cells (RBCs), abnormal RBC morphology, and a shortened RBC lifespan, which results in ineffective erythropoiesis. Disease severity in thalassemia syndromes varies from mild, non-transfusion-dependent thalassemia (NTDT) to severe transfusion-dependent thalassemia (TDT).

Nearly 100,000 symptomatic patients with beta-thalassemia major are born each year, predominantly in low- and middle-income countries (LMIC)[1]. Regular blood transfusions and iron chelation therapy represent the cornerstone of managing transfusion-dependent thalassemia (TDT) patients in these regions[2]. Unfortunately, allogeneic stem cell transplantation, the sole curative intervention, remains largely inaccessible to the majority of thalassemia patients in LMICs[2].

The spleen assumes a pivotal function in the elimination of aberrant red blood cells (RBCs) from the circulatory system. Nevertheless, splenomegaly can lead to a reduction in RBCs, platelets, and white blood cells (WBCs). Inadequate transfusion protocols in thalassemia precipitate extramedullary hematopoiesis within the spleen, resulting in splenic enlargement and hypersplenism. Consequently, splenectomy is frequently warranted to mitigate this complication and diminish the necessity for blood transfusions [3,4]. However, splenectomy is concomitant with enduring complications, including recurrent infections, an elevated risk of thromboembolism, and pulmonary hypertension[2]. Our objective was to investigate the indications of splenectomy and prevalence of post-splenectomy complications in transfusion-dependent thalassemia (TDT) patients from a single center in a Thalassemia Day care of an Urban area of west India.

Materials and methods

This retrospective study was conducted at the Thalassemia Clinic of a tertiary care teaching hospital and research center in Western part of India. Following approval from the institutional ethics committee [IEC-LTH 08/2023/], we reviewed the medical records of transfusion-dependent thalassemia (TDT) of patients registered at the clinic between July 2017 to January

2024. All the patients registered in the thalassemia clinic undergo annual assessments for endocrine function, transfusion-transmitted infections including hepatitis B, hepatitis C and human immunodeficiency virus, hepatic and cardiac iron overload using T2 * Magnetic resonance imaging (T2*MRI), echocardiography, and bone mineral density. Monthly tests include Complete blood count, Liver function test and Renal function tests and Serum ferritin levels are done every 6 monthly.

All TDT patients who had undergone splenectomy during the study period were included in the analysis. A small subset of patients who underwent splenic embolisation were excluded from the study. All patients received an additional dose of the Pneumococcal 10 vaccine four weeks prior to the scheduled pre-splenectomy vaccinations. As per institutional protocol, all individuals were administered a single dose of pneumococcal conjugate vaccine and a single dose of meningococcal conjugate vaccine (A, C, Y, W) six weeks before the splenectomy. We examined patient demographics, clinical characteristics, haematological parameters, and annual transfusion requirements at the most recent follow-up, as well as rates of splenectomy-related complications—such as post-splenectomy infection, thrombosis, and pulmonary hypertension.

Definitions

TDT was defined by a requirement of regular packed RBC transfusions within eight weeks (6–24 units of packed RBCs per year). The diagnosis of pulmonary hypertension was based on the peak tricuspid regurgitation velocity (TRVmax) of an echocardiogram performed by a cardiologist and or by 2015 ESC guidelines [5]. Patients with high echocardiographic probability (TRVmax values in the range of 2.9–3.4 /s, along with the presence of other echo “pulmonary hypertension signs” or TRVmax values >3.4 m/s) were considered indicative of pulmonary hypertension. Thrombosis included both arterial and venous thrombosis based on history and confirmed by imaging. Post spleenectomy infection was defined as any fulminant sepsis, meningitis or pneumonia triggered mainly by *S. pneumoniae* followed by *H. influenzae* type B and *N.* meningitidis [6].

We analyzed iron-overload-related complications, including cardiovascular disease, endocrinopathy, and decompensated liver disease. Cardiovascular disease in thalassemia patients was defined by the occurrence of decompensated heart failure, echocardiographic evidence of left ventricular dilation and reduced contractility, or clinically significant arrhythmias. Endocrinopathies included both subclinical and clinical cases of hypothyroidism, hypogonadism, hypoparathyroidism, insulin-dependent diabetes mellitus, and adrenal insufficiency, as confirmed by biochemical investigations. Decompensated cirrhosis was identified by any deterioration in liver function, characterized by jaundice, ascites, hepatic encephalopathy, hepatorenal syndrome, or variceal bleeding.

Statistical analysis

Continuous variables were expressed as median and range, and categorical variables were expressed as percentages. Post-splenectomy overall survival analysis was done using the Kaplan-Meier method. Haematological parameters and yearly transfusion volume (ml/kg/year) at one-year pre-splenectomy versus post-splenectomy at the last follow-up were compared using a *t*-test. P-value < 0.05 was considered to be significant. All the statistical analyses were done using Prism Version 10.2.3.403.

Results

Till January 2024, 304 thalassemia patients were registered in the Thalassemia Day care centre of whom 15 were TDT and splenectomised. Three patients who had splenic artery embolisation were excluded from the analysis. The patients' median age at the start of chronic transfusion therapy was nine months (range 3 months – 18months). The median age of the patients at the time of splenectomy was 14 years (range 6– 22 years).

Out of 304 patients, 15 patients underwent spleenectomy. Among these, 11 individuals were diagnosed with Thalassemia major, while 3 patients presented with Thalassemia intermedia, which subsequently progressed to Transfusion-Dependent Thalassemia (TDT) by the age of 10 years. Additionally, 1 patient was identified as having HbE-Beta Thalassemia which was transfusion dependant. All patients underwent open splenectomy, with two individuals also undergoing concomitant cholecystectomy. The primary indications for splenectomy included symptomatic splenomegaly and a progressively increasing frequency of packed red blood cell (PRBC) transfusions, exceeding an annual volume of 258 ml/kg, (180−370) despite receiving adequate iron chelation therapy. All patients were administered post-splenectomy penicillin prophylaxis.

The median pre-transfusion haemoglobin at the last follow-up was significantly higher in our cohort than at one-year pre-splenectomy (9.5 g/dl versus 6.4 g/dl, $p < 0.001$). Also, the median total leukocyte and platelet counts at the last follow-up were elevated compared to the one-year pre-splenectomy values ($p < 0.001$). The median yearly transfusion volume at the time of the last follow-up was decreased compared to one-year pre-splenectomy (145ml/kg/year versus 278 ml/kg/year, $p < 0.001$).

Table 1: depicts the demographic and clinical characteristics of the splenectomised TDT patients, including the long-term complications and causes of mortality.(N=15)

Parameters			Median (Range) N=15 (%)
Males			12 (80)
Females			03(20)
Age in years at splenectomy			14(6−22)
Age in months at the start of chronic transfusion therapy			9 (3–18)
Haematological parameters	One-year pre-splenectomy Median (Range)	Last-follow-up post-splenectomy Median (Range)	P value
Pretransfusion haemoglobin (g/dl)	6.4 (5.4–8.2)	9.5 (7.5–11.2)	<0.001
Total leukocyte count (x 109/L)	2.94 (1.4–6.4)	19.4 (11.2–50.4)	<0.001

Parameters			Median (Range) N=15 (%)
Platelet count (x109/L)	82 (26−187)	504 (102–1321)	<0.001
The volume of transfusion (ml/kg/year)	258 (180−370)	145 (140 –250)	<0.001
Iron overload status at last-follow-up post-splenectomy			Median (Range) N (%)
Ferritin (ng/ml)			3506.5 (1100–14220)
Myocardial iron concentration on T2*MRI(msec)			20.05 (3.65–62.4)
Liver iron concentration on T2*MRI (mg/gm)			11.5 (0.5 –84.9)
Type of surgery/intervention			N (%)
Open splenectomy			15 (100%)
Concomitant cholecystectomy with splenectomy			02 (13.3%)
Antimicrobial prophylaxis			N (%)
Presplenectomy vaccination			15 (100)
Post-splenectomy penicillin prophylaxis			15 (100)
Long-term complications			
Thrombosis			02 (13.3%)
Pulmonary hypertension			03 (20%)
Post spleenectomy Infections			01 (6.6%)
Iron overload-related complications			
Cardiovascular disease			06(40%)
Endocrinopathy			04 (26.6%)
Decompensated Chronic liver disease			03 (20%)
Death (sepsis Post spleenectomy)			01 (6.6%)

Long-term complications in splenectomised patients

Thrombosis was noted in 2 (13.3%%) patients, including 1 case of ischemic stroke and 1 case of portal vein thrombosis. These 2 patients developed thrombosis after 4- and 6 -years post-splenectomy, respectively. All post spleenectomy patients whose platelet counts were more

than 1000 x $10^9/L$ were started on Aspirin prophylaxis at the dose of 5 mg/kg/day to maximum of 75 mg per day. Pulmonary hypertension was noted in 03 (20 %) patients.

Only one patients developed post splenectomy sepsis after one year of splenectomy and died due to it. All patients were on penicillin prophylaxis. The single patient had persistent pancytopenia with allo - immunization who developed early sepsis and died within one year of splenectomy. The diagnosis of post spleenectomy sepsis was based on the fulminant clinical presentation, however, microbiological diagnosis could not be obtained in any of the patients.

The iron-overload-related complications noted in our cohort were cardiomyopathy in 6 (40 %), endocrinopathy in 4 (26.6 %), and chronic liver disease in 3 (20 %). The median age at the start of the chelation therapy was 13 years (range 2.5–22) years. The median ferritin level at the last follow-up was 3506.5 (range 1100–14,220) ng/ml. At the last follow-up, the median liver iron concentrations were 11.5 (0.5 –84.9) ng/ml. The median myocardial T2 * value was 20.05 (3.65–62.4) msec. We also analysed the chelation practices in our cohort and found that 55 (53.4 %) patients were on irregular chelation therapy. The reasons for irregular chelation were drug inaccessibility in 9 (60%) and busy schedule/forgetfulness in 6 (40%). The patients who developed thrombosis were not compliant with Aspirin prophylaxis.

Discussion

We retrospectively assessed the Indications, long-term efficacy and complications of splenectomy in a large cohort of TDT patients from a low- and middle-income country (LMIC). The majority of these patients underwent splenectomy during childhood or adolescence. While splenectomy proved effective in optimising pre-transfusion haemoglobin levels and reducing the need for transfusions over time, splenectomised TDT patients continued to experience significant long-term complications related to iron overload, in addition to risks such as, thrombosis, and pulmonary hypertension.

Almost half of the patients had their pre-transfusion haemoglobin elevated to 9. 5 g/dl or more at the time of analysis. This indicates achieving the therapeutic target as recommended by the Thalassemia International Federation (TIF) of pre-transfusion haemoglobin 9.5–10.5 g/dl post-splenectomy in our patients [2]. The yearly transfusion volume decreased from 258 ml/kg/year at 1-year pre-splenectomy to 145 ml/kg/year at the last follow-up. Several studies have demonstrated reduced transfusion requirements immediately after splenectomy. In the study by Merchant et al., transfusion requirements decreased from 294.85 ± 22.6 ml/kg/year pre-splenectomy to 138.41 ± 90.38 ml/kg/year at one year after splenectomy ($p < 0.01$), and this difference in transfusion volume was maintained after five years ($p < 0.01$) [7]. Akca et al. demonstrated a heterogeneous response to splenectomy in patients with Thalassemia Major. While a significant diminution in the mean annual transfusion volume was observed at both one year and five years following splenectomy, none of the patients achieved a complete response. Partial responses were documented in 32.3% and 35.8% of the patients at one and five years, respectively[8]. Osataphan et al. also showed decreased transfusion requirements and improved haematological parameters after splenectomy [9]. HbH disease and splenectomy performed after the age of ten emerged as the principal predictors of therapeutic efficacy. This indicates that a milder form of

thalassemia correlates with a superior hematological response to splenectomy[9]. Several studies have substantiated the enhancement in quality of life consequent to a reduction in transfusion requirements following splenectomy[10]. Pulmonary hypertension and thromboembolism remain the two major long-term complications in thalassemia patients undergoing splenectomy [2]. The incidence of pulmonary hypertension in splenectomised thalassemia patients varies from 5 % to 30 % [11]. In our study, approximately 3 i.e. 20 % of the patients had pulmonary hypertension. We employed echocardiographic parameters, such as the maximum tricuspid regurgitant velocity (TRVmax), to diagnose pulmonary hypertension. The gold-standard approach is right heart catheterization which was not utilized due to logistical and financial constraints.

Ischemic stroke and DVT were the main thrombotic complications noted in our patients. Splenectomised thalassemia patients have a greater venous and arterial thrombosis risk, including silent cerebral infarctions (SCIs). The risk is notably higher in NTDT patients [12]. Ischemic stroke is more common in TDT, while SCIs are more frequent in NTDT patients. The cumulative incidence of ischemic stroke and SCI in thalassemia is 1.13 %, a risk factor for long-term cognitive impairment and neurological deficits [13]. Splenectomy thalassemia patients have an increased proportion of platelets and nucleated RBCs rich in adhesion molecules in the circulation, increased thrombin generation and reduced levels of natural anticoagulants, which add to the hypercoagulable state [14].

Only one patient, 6.6 % had severe sepsis in our cohort who died due to infection. Although post splenectomy sepsis is commonly reported within three years of splenectomy, there are case reports where it happened up to 20 years after splenectomy. The prevalence of post splenectomy sepsis is 0.1–0.5 %, and the mortality rate is up to 50 % [15]. Recent guidelines recommend immunisation against Streptococcus pneumoniae (pneumococcus), Neisseria meningitidis (meningococcus), and influenza for patients who have undergone splenectomy [16]. Vaccination against Haemophilus influenzae type b (Hib) may also be considered, depending on regional incidence rates. Lifelong antibiotic prophylaxis with oral penicillins or macrolides should be considered for patients at an ongoing high risk of pneumococcal infection [16]. Greater emphasis should be placed on educating patients and healthcare providers about the risk of sepsis and its prevention, particularly in splenectomised thalassemia patients. splenectomised patients had a higher incidence of myocardial iron load (48%) and higher myocardial iron compared to non-splenectomised patients (28%) [17]

Conclusion

Splenectomy significantly reduces transfusion requirements in TDT patients but is associated with risks such as thrombosis, pulmonary hypertension, and sepsis. Long-term mortality is primarily driven by iron-overload-related cardiomyopathy.

Limitations of the study

Our study has multiple limitations. First, it is a retrospective single-centre study with a few missing records and data. The absence of comparison with non-splenectomised TDT patients was another major limitation. Also, post-splenectomy survival is impacted by irregular chelation and resultant iron overload-related complications

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